COMMENT

The prejudices of the past arose largely from inadequate evaluation of the surgical risk and resultant disasters. Any patient is a surgical risk; the one afflicted with a chronic disease such as tuberculosis is substandard and should be evaluated most painstakingly and surrounded by every safeguard before, during and after the operation. Modern methods of diagnosis, refined and adept surgical technique and, above all, a trained anesthetist render all surgical procedures less problematical. There must be unremitting attention to the infinite details which experience has demonstrated are such important factors in the treatment of tuberculosis at every stage. The avoidance of fear and consequent psychic shock weigh even more heavily here than in the case of the average. The subnormal patient requires days or weeks of preparation, and a long period of postoperative rest for recuperation. Speed in operating, avoidance of hemorrhage or undue trauma,[10] maintenance of uniform body temperature, and a properly administered anesthetic are factors contributing to safety.

While local anesthesia[4 5 9] is generally growing in favor among surgeons, should an inhalation anesthetic be decided upon, the choice of the anesthetist is of vastly greater importance than the kind of anesthetic to be used.[6] The occasional anesthetist is just as dangerous as the occasional surgeon. Unhappy results following a general anesthetic usually imply incompetence in its administration. True ether pneumonia from the irritation of the lung by the anesthetic is comparatively rare, but postoperative pneumonia may readily occur, due primarily to aspiration of infectious material.[7 8 13] To maintain the cough and swallowing reflex, nature's safeguards, is the ideal to be attained. A higher percentage of pulmonary complications follow local anesthesia than general anesthesia.[12] The use of atropin, preliminary to ether in tonsil surgery, operating with the patient in a lateral, slight Trendelenburg, or Rose position, are protective measures. Safety lies in good judgment, skill and teamwork—all available in the modern large sanatorium.

CONCLUSIONS

Although unnecessary surgery is never to be recommended, and the possible surgical risk in every operation, however slight, should never be minimized, results as revealed in a careful analysis of one hundred instances of operations on the upper air passages of patients with pulmonary tuberculosis give little support for a pessimistic attitude. When there is definite indication for a rational surgical procedure for the relief of pain or discomfort, or for the removal of an actual focus of infection, the presence of a pulmonary tuberculous lesion should not be considered an absolute contraindication.

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REFERENCES

1. Boone, John C.: Tonsillectomy in Pulmonary Tuberculosis, J. Indiana M. A., 20:518, No. 12.
2. Abbott, Wilson R.: The Value of Surgical Intervention upon the Tuberculous and the Importance of the Selected Anesthetic, Anesth. and Analg., 7:34-37, No. 1.
3. Brooks, J. D.: The Tuberculous Patient as a Surgical Risk, U. S. Vet. Bureau M. Bull., p. 453 (May 30), 1930.
4. Milincoff, A. E.: Anesthesia in the Tuberculous, U. S. Vet. Bureau M. Bull., p. 700 (July 27), 1930.
5. Miller, Felix P.: Surgery and Anesthesia of the Tuberculous, Anesth. and Analg., 7:1154, No. 3, 1928.
6. Griffith, F. Webb: Surgery and Anesthesia of the Tuberculous, J. Anesth. and Analg., 6:200, No. 4.
7. Anesthesia in Tonsillectomy, Editorial J. Indiana M. A., 21:525, No. 12.
8. Hara, H. J.: Aspiration in Tonsillectomy, California and West. Med., 33, No. 3 (Sept.), 1930.
9. Brown, Gilbert: Anesthesia in Relation to Lung Disease, J. Anesth. and Analg., p. 381, 1929.
10. Struthers, J. E.: Surgical Management of Exophthalmic Goiter, A. J. Tbc., 20:257, 1929.
11. Brooks, J. D.: Spinal Anesthesia in the Tuberculous, U. S. Vet. Bureau M. Bull., p. 700 (July 27).
12. Grondy, Charles R.: Ether Anesthesia in Cases of Pulmonary Tuberculosis, A. R. Tbc., 16:265, 1927.
13. Botsford: Post T. Pul. Abscess, J. California and West. Med., 21:19, No. 1.

LEUKOPENIA—A REVIEW: WITH SPECIAL REFERENCE TO AGRANULOCYTIC ANGINA*

PART I

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INTRODUCTION.—This subject is not only timely but it seems to me it is appropriate for this hall and occasion in that it leads us into the same fields of pathology, clinical pathology and research in which he whose name these lectures bear performed such valuable service.

The white cells of the blood form one of the important defenses of the body; their usefulness is sure in certain fields and we have reason to suspect a still greater importance in other directions as yet unproven. Any failure of such an essential bulwark of the body is at once a serious matter demanding our attention. We are familiar with the tragic results when leukocytosis fails in septic infections and pneumonia, and within recent times an apparently new and often fatal syndrome, agranulocytic angina, seems to be becoming increasingly common. Also we are encountering more instances of intense leukopenia apparently resulting from the use of modern chemicals in therapy. Is it possible that the human race is threatened with a weakening of this form of body defense or with a failure of this defense against newly developed dangers? Is it conceivable that civilization by reducing the incidence of minor injuries and infections thus lessens the frequent demands which are necessary to maintain a defense at its highest efficiency,

* Stanley P. Black Memorial Lecture delivered at Pasadena, January 12, 1931.

Editor's Note.—The annual Stanley P. Black Memorial Lecture at Pasadena is given in memory of the late Stanley P. Black, a graduate of Northwestern, class of 1887, who came to California in 1897. Doctor Black was professor of pathology in the College of Medicine of the University of Southern California, was health officer of Pasadena for years, and at all times maintained an active interest in public health work. He had much to do with the Certified Milk Commission of Los Angeles. After his death on February 4, 1921, his friends united in getting up a memorial fund, which sponsors the annual Stanley P. Black Memorial Lecture.

and at the same time through the increasing exposure of all of us to chemicals, either in fumes, in medicines, or other contacts, brings about a further depression of the already weakening function of defense of the body through the white cells of the blood?

The Normal White Blood Cell Range.—In the normal adult the number of white blood cells ranges between 5000 and 10,000 per cubic millimeter; above 10,000 justifies the term "leukocytosis"; below 5000 the term "leukopenia."

Within the normal range the count swings up and down with little or no change in the percentage figures of the various types of white cells which together make up the total count. Greater increases or decreases in the total count are, as might be expected, usually chiefly due to increases or decreases in the number of cells of the most numerous form, the so-called polymorphonuclear neutrophil or neutrophilic granular leukocyte or, familiarly, 'polies.'

For our purposes tonight it is important for us to remember that this cell type arises wholly in the bone marrow where its immature forms, the myeloblast and myelocyte, normally remain, and that it forms from 60 to 70 per cent of the total white cells of the blood.

Leukocytosis.—Leukocytosis may be due to an increase of other cell types as, for example, the eosinophilic leukocytosis of trichiniasis; but severe leukopenia cannot occur unless the neutrophilic leukocytes are diminished. Often all the cell forms are coincidentally reduced in number. Perhaps the most marked leukopenia not due to a reduction in neutrophils is that due to a reduction in the number of lymphocytes by radiation.

Leukopenia.—It would seem that leukopenia might come about in three ways, either an increased destruction or a failure of production, or a migration of the cells from the peripheral blood from which our clinical counts are made.

No form of leukopenia has been proved to be due wholly to an increased destruction of leukocytes, although such may well occur, and this factor may play a part in many leukopenias.

Failure of production seems to be a frequent mechanism in bringing about leukopenia. Sometimes the reduction of white cells is but one manifestation of bone marrow failure, in others the white cells alone are affected, in still others the white cells and the platelets. Aplastic anemia is a good example of the first form; in its fully developed picture there is not only anemia, but also leukopenia and reduction in platelets. Red cells, platelets, and leukocytes of marrow origin are all reduced, and only the lymphocytes and monocytes retain their usual numbers.

Leukopenia from redistribution of white cells is the third variety. Usually it is a transitory phenomenon although it may be quantitatively very striking; usually it results from the entrance of a foreign protein substance into the blood.

It is the granular leukocytes, especially those with neutrophilic granules, which leave the peripheral blood and are found in large numbers in the internal organs, especially the liver and spleen.[1] The reduction in count in the peripheral blood under these conditions may be very great as but few of the usually numerous representatives of the granular series of white cells may be left in the peripheral blood. The mechanism of the phenomenon has been much discussed; Bull,[2] who studied it following the injection of typhoid bacilli, believes that the white cells collect in the organs the better to engulf the circulating bacteria. Whatever the mechanism may be, the phenomenon is very rapid and constant. The count of white cells in the peripheral blood often falls within an hour after an intravenous injection of killed bacteria or other foreign protein to a quarter, or even less, of its former level. Subsequently, a leukocytosis appears which may exceed 20,000 per cubic millimeter within twenty-four hours. This leukocytosis is largely formed of young cell forms,[3] but there is no sure evidence that the cells which leave the peripheral circulation during the period of leukopenia do not return.

Miller and I attempted to solve the problem by studying the excretion of nitrogen in rabbits injected with dead typhoid organisms. The total nitrogen, urea nitrogen, and allantoin nitrogen, which is in rabbits the end product of nucleic acid breakdown, equivalent to uric acid in humans, were determined. With dead organisms we obtained no change in excretion, even when very great changes in the white cell counts occurred.

ETIOLOGY OF LEUKOPENIA

These theories of how leukopenia is brought about are the only ones we have to turn to in trying to explain the various forms of leukopenia which we encounter.

1. *Infectious Leukopenia.*—A few infections as, for example, typhoid fever, do not show leukocytosis; a very few dengue, kala azar, and smallpox up to the fourth day give an actual leukopenia. We have no criteria to tell us which infection will have leukocytosis; which, leukopenia. We might reason that a foreign protein enters the blood in malaria and that in low-grade chronic infection an almost symbiotic relationship between the infecting agent and the host exists, but these arguments help us little, with other diseases.

In sharp contrast to the failure of a low-grade infection to excite leukocytosis is the leukopenia resulting from an overwhelming infection of a type which in less severe form would cause marked leukocytosis. This phenomenon is usually encountered in cases with heavy infection by streptococci, pneumococci, or staphylococci.

This form of leukopenia has long been recognized; it was in earlier days described as the "lymphocytosis of sepsis" on account of the relative lymphocytosis which the differential count reveals when the granular neutrophils are markedly reduced. There is no increase in the actual numbers of lymphocytes, but a high percentile rise. To emphasize this relative lymphocytosis, as was formerly done, is unfortunate, for the important change is the fall in the cells of the granular series.

We do not know for a certainty whether this type of leukopenia is due to depression of marrow function or whether the granular cells leave the peripheral blood to congregate in the internal organs, or even if these cells are destroyed. It is commonly assumed by writers that it is the failure of the marrow to maintain the production of cells which accounts for the leukopenia, and such evidence as there is does favor this view, but it is not settled. In favor of the redistribution hypothesis is the fact that such leukopenia usually only occurs when a heavy blood stream infection is present.

It is important to realize that a degree of infection which would excite leukocytosis in one individual would be overwhelming to an asthenic debilitated or elderly person. It is also important not to apply this explanation of leukopenia too readily in all instances, as for example, in agranulocytic angina. The assumption that this syndrome is the result of such an overwhelming infection is, to my mind, wholly untenable in the face of many facts and observations, notwithstanding the wide support prematurely given to this assumption.

2. *Leukopenia in Diseases of the Hemopoietic System.*—Aplastic anemia has been mentioned as the clearest example of leukopenia due to bone marrow failure. The same is true in pernicious anemia, osteosclerotic anemia, and aleukemic leukemia at times. The leukopenia of some stages of Banti's disease is not easily explained.

3. *Toxic Leukopenia.*—A variety of chemicals cause leukopenia, of which benzol and arsenic are the best known; benzol because of its therapeutic use in lowering the white cell count in leukemia, arsenic because of its widespread employment in many processes and treatments, especially in the form of arsphenamin in syphilis.

Benzol seems to act by depressing bone marrow function and so do the x-ray and radium. The anemia, and sometimes thrombopenia, which may appear coincidentally with the leukopenia, seem to support this view.

Arsphenamin leukopenia is more interesting, and deserves special emphasis in view of the temptation to use this medicament intravenously in agranulocytic angina because of the discovery of Vincent's organisms in the ulcers of the mouth and throat.

D. L. Farley,[4] of our university staff, has recently collected a series of thirty-nine cases of leukopenia following arsphenamin therapy; twenty-three of these died. He concludes that no one type of arsphenamin is more apt to produce leukopenia than another and he believes that the direct cause is disintegration in vivo of the arsphenamin so that a benzol-like action takes place. The infrequence of the occurrence suggests that there must exist a preceding weakness of the hemopoietic apparatus in the individuals affected.

The most important point that Farley makes is that one should be alert to recognize early symptoms of bone marrow weakness in patients who are to receive arsphenamin treatment. This suggestion is interesting in view of the free use which some have made of arsphenamin in the treatment of agranulocytic angina.

4. *Allergic Leukopenia.*—I have quoted some of the experimental results in the production of leukopenia by intravenous injection of foreign protein. Much the same results occur in nonspecific protein therapy. The promptness, magnitude and duration of the blood count changes differ with the protein employed.

We are not sure whether or not a similar leukopenia may not occur from the spontaneous entrance of foreign protein either in health or disease. Widal's so-called hemoclastic test of liver function is based on the assumption that a diseased liver permits insufficiently broken-down food protein to enter the circulation. The resultant leukopenia is interpreted as evidence of this disturbed hepatic function. This is unproved, but it is theoretically possible that leukopenia may occur in the absence of actual injection of a foreign protein and without the striking phenomena of protein shock. I emphasize this for further mention in discussing theories which might explain agranulocytic angina.

IDIOPATHIC LEUKOPENIA—AGRANULOCYTIC ANGINA

5. *Idiopathic Leukopenia.*—Having mentioned the commoner forms of explainable leukopenia, let us turn at once to that unexplained form which is commonly termed *agranulocytic angina.* Perhaps this term, given by Friedemann, is not the best name for the syndrome described by Schultz[5] in 1922, but it is certainly that most commonly in use in this country.

Of course, Schultz was not the first to see instances of this syndrome; since his description of it, many older case reports have been found which agree more or less accurately with it. The importance of Schultz' contribution resides in the fact that he realized that the cases which he reported differed from the usual instances of angina on the one hand, and from the recognized cases of leukopenia on the other. Whether or not he was right in believing that the condition was a clinical entity matters little; what does matter is that he distinguished these cases from those in which leukopenia results from intense sepsis or other causes.

It is quite unfair to Schultz to make out that Türk[6] in 1907 described this syndrome. The cases of severe sepsis with low white cell counts which he described perhaps included one or more instances which would today be classed in this syndrome group, but Türk did not distinguish them from the commoner leukopenia of overwhelming infection. However, the *Journal of the American Medical Association,*[7] in a recent leading editorial, certainly gives the other impression and so do a number of writers of current articles.

Once attention was drawn to the syndrome by Schultz the tide turned to the other extreme and the literature has been flooded with reports of cases under this diagnosis which were, in fact, nothing more than the well known leukopenia of intense infection, formerly called "lymphocytosis

of sepsis." Much confusion has arisen from this and also from the uncertain terminology. Blumer [8] of Yale did his best to combat this confusion by an article entitled "The Agranulocytic Blood Picture in Conditions Other Than Angina" in which he reminded us that leukopenia occurred in sepsis and other conditions besides agranulocytic angina.

We are now in the stage in which the original definition of the disease is being extended and altered through the recognition of an unexpectedly large number of cases, many of which differ in some respects from the picture described by Schultz. His six cases were all in middle-aged women, living under institutional conditions, all developed gangrenous lesions of the mouth or pharynx, all had fever, and there was a fatal outcome in each. In each a sharp leukopenia was observed. We now know that males may be affected, that lesions may occur along the intestines and in the rectum or vagina, and that all cases are by no means fatal. Our conception of the condition has changed, but we are still in ignorance of its cause. Let me postpone discussion of the various theories on this point until we have discussed the other features of this interesting malady.

Pathology.—Two kinds of lesions seem sufficiently constant to be accepted unreservedly; the first of these includes the ulcers seen during life in the mouth, the pharynx, the larynx, the rectum or vagina, and found at necropsy at various points along the gastro-intestinal tract. In the mouth it is at the gingival margin that ulcers seem most common, and in the throat it is the tonsils and the pharyngeal pillars which are involved. Rarely the skin is involved; I have seen necrotic areas develop at the finger-nail edge, where the patient had picked or bitten at hangnails.

Wherever the lesion, it possesses similar characteristics; it is a necrotic process, with little or no reactive erythema about it. This has been more evident in the gingival lesions than in those of the pharynx, although even there the lesions have a distinctive appearance. Dr. Fielding Lewis, who has seen several of these cases with me, feels sure he can diagnose the syndrome from the local picture in the throat, and also feels that he never saw this throat picture until the past few years.

The tissue looks dead and its subsequent sloughing out bespeaks its necrotic state. Perhaps I have imagined it, but it has seemed to me that with improvement in the blood count and general condition, there occurred an increase in the reactive erythema about the lesions. In a case which is doing badly the tissues almost melt away. Neighboring lymph nodes enlarge and become painful, and the spleen may enlarge considerably. The liver also may enlarge, and jaundice has occurred in perhaps half of the reported cases.

The other lesion concerns the bone marrow, and here the evidence is less clear. In the first place, the bone marrow is, of all tissues, that most difficult to be dogmatic about. In the second place, one must be cautious not to be led into describing, on perhaps inadequate evidence, findings which on theoretical grounds one might have been anticipating. Be that as it may, the literature seems to justify the statement that the bone marrow in agranulocytic angina is distinctly abnormal.

It has been described as grossly liquid and of a variety of colors ranging from yellow to red. Specimens obtained by sternal puncture during life or at autopsy have shown varying degrees of hypoplasia with scattered patches of necrosis. Few, if any, of the progenitors of the granular leukocytes, the myeloblasts and myelocytes, are present and no adult granular leukocytes are seen. In sharp contrast the erythrogenetic centers are normal, although the red color of the marrow is more often due to hemorrhage than to hyperplasia of the red cell forming centers. This term is an unfortunate one for it implies a general hyperplasia of all three bone marrow elements, while the actual state may affect only the production of erythrocytes and not the platelets or leukocytes.

Also in agranulocytic angina the parent cells of the platelets are usually present in normal numbers although some of the individual cells may show degenerative changes. Such myeloblasts and myelocytes as are present are badly degenerated.

Probably an occasional case will show a hypoplasia of erythroblasts or of megakaryocytes or both, for cases have been reported with anemia and with thrombopenia. Such cases obviously approach closely the picture of aplastic anemia.

Doctor Baldwin Lucke of our pathological department has also observed and described a necrosis of the intimal and muscle layers of the smaller arteries much like that seen in so-called malignant hypertension.

Laboratory Data.—The urine is that of any febrile condition; the feces may contain blood if ulcers of the bowel are present.

Interest centers on the blood count. The hemoglobin and the red cell count may be normal, and the early presence of anemia suggests a preceding cause. A few cases are on record with unexplained severe anemia, but these are open to the suspicion of being instances of aplastic anemia. Anemia has played no part in the cases which I have seen, but in each we have employed frequent transfusions. In fact, plethora and polycythemia have worried us more than anemia.

The number of platelets has been normal in some cases, low in others. Unfortunately the majority of reports contain no count of platelets. In our case Mrs. S. the lowest figure was 67,000. Kastlin [9] reports that the platelet count was normal in twenty of twenty-seven cases collected by him from the literature, but no figures are given and it is probable that the cases were of various kinds of leukopenia inasmuch as one of the two personal cases reported followed upon the injection of arsphenamin. Allan's [10] case had a platelet count of 15,000 and a widespread purpura. Aubertin and Levy [11] include thrombopenia as a constant feature of the condition, while Friede-

mann states that in all his cases the number of blood platelets was normal or increased. More data is needed on this point.

It is the white cell count which is most important. At the height of a severe attack the picture is easily described; the total count is down to 1000 or less. Counts as low as 400 are not uncommon. The lower the total count the fewer granular leukocytes, neutrophilic, eosinophilic, or basophilic are seen; while with a very low total count often none may be discovered in a prolonged search of the stained blood film; only lymphocytes and monocytes are present. When, for example, the differential count reads 90 per cent of lymphocytes and 10 per cent of monocytes and the total count is 800, there is not only an absence of granular cells but a distinctly reduced number of lymphocytes and monocytes present.

When only an occasional granular leukocyte is seen, the cells are apt to appear irregular and poorly stained as though damaged.

At first it was thought that the leukopenia followed the angina; now it is recognized that often, if not always, the white count drops before the onset of systemic or ulcerative symptoms appear. Apparently the onset of leukopenia precedes other symptoms by several days and some have attempted to relate this period to the assumed duration of life of the leukocyte, which is about four days. It is suggested that the count does not reach its lowest level until four days after the marrow has ceased to produce cells. During this period the cells already in the circulation die off. Many records agree that the early drop is gradual and not severe; early counts give figures of from 4000 to 2000. If the attack progresses, the leukopenia becomes more marked, the last count before death often being the lowest. If the attack proves mild, the leukopenia never becomes very severe, and if the attack aborts without going on to ulceration the count may drop no further and may, in fact, soon rise.

Improvement in symptoms, local or general, is always preceded or accompanied by a rising white count, but convalescence may continue while the white count remains in the neighborhood of 5000. Evidence supports the assumption that during the period of rising count young granulocytic forms are first to appear and are present in greater than normal percentages until time sufficient for them to mature has elapsed.

(To be continued)

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REFERENCES

1. Goldscheider and Jacob: Ztschr. f. klin. Med., 25:373, 1894.
2. J. Exper. Med., 22:475, 1915.
3. Pepper and Miller: J. Infect. Dis., 19:694, 1916.
4. Am. J. M. Sc., 179:214, 1930.
5. Deutsche med. Wchnschr., 48:1495, 1922.
6. Wien. klin. Wchnschr., 20:157, 1907.
7. J. A. M. A., 95:1428, 1930.
8. Am. J. M. Sc., 179:11, 1930.
9. Am. J. M. Sc., 173:799, 1927.
10. Ann. Int. Med., 2:542, 1928.
11. Arch. d. Mal du Coeur, 21:353, 1928.

DEAFNESS—A VITAL SOCIAL ECONOMIC AND MEDICAL PROBLEM*

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DISCUSSION *by Isaac H. Jones, M. D., Los Angeles; Ferris Arnold, M. D., Long Beach.*

MY object in presenting a discussion of a topic so old and time-worn as deafness is to bring before you, if possible, a very practical discussion of the needs of the deafened and our responsibilities as physicians in the rehabilitation of the deafened.

THE NOMENCLATURE "DEAFENED"

In dealing with this subject I have chosen the latest nomenclature, using that broader and more inclusive word "deafened" instead of deaf.

Dr. Alexander Graham Bell, famed inventor of the telephone, whose work in the aid of the deafened has given him the honored title of "patron saint," always referred to the condition as "imperfect hearing," rather than "hard of hearing." His own wife was for many years one of the incurably deafened.

Primitive peoples destroyed their deafened and blind, or held them in awe, keeping them locked up or in seclusion, as they did their insane. A deafened person was regarded as a family encumbrance and a great disgrace. Later they were allowed to live, but were treated with great cruelty. In Holy Writ we read that "The Lord commanded Moses, saying, Speak unto all the Children of Israel and say unto them, Thou shalt not curse the deaf, nor put a stumbling block before the blind, but shall fear thy God."

Under Roman law, persons born deaf were deprived of all civil rights and were required to have guardians.

THE HANDICAP OF DEAFNESS

Deafness, no matter how slight, is a mountain some cannot climb.

Few learn to accept the handicap gracefully. In fact practically everyone who acquires deafness goes through "hell" mentally, physically and unfortunately in most instances, economically.

If any one of us should try going about with our ears stuffed with cotton, shutting out all pleasant sound, we would better appreciate the handicap of the deafened and the tragic plight of the person, child, or adult who has lost, or is losing, his hearing.

Seventy-five years ago Sir William Wilde, a noted Dublin aurist, summed up deafness in one aphorism: "There are two kinds of deafness—one due to wax, which is curable; the other is not due to wax and is not curable." Is it not a regrettable fact that, with all our modern study concerning chronic deafness, this statement is still so largely true?

In the realm of specialized medicine the otologist has accomplished much in the treatment of the sick both medically and surgically, but in cases

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